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Congenital Diaphragmatic Hernia Overview

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Summary

Disease characteristics. Congenital diaphragmatic hernia (CDH) is characterized by incomplete formation/muscularization of the diaphragm resulting in apparent absence of the diaphragm or eventration (elevation of a portion of the diaphragm that is thinned because of incomplete muscularization). Diaphragmatic hernias include posterolateral (Bochdalek), Morgagni and other anterior hernias, and central hernias. About 50-60% of affected individuals have isolated CDH; the remainder have complex CDH, that is, CDH occurring with additional malformations or as part of a single gene disorder or chromosome abnormality. Infants with CDH often present in the neonatal period with severe respiratory distress; pulmonary hypoplasia is common. Presenting symptoms after infancy can be acute onset of respiratory or gastrointestinal distress or abdominal pain from chronic intestinal obstruction or pleural effusion from entrapment of the bowel in the chest.

Diagnosis/testing. Clinical examination of the newborn with CDH often reveals a scaphoid abdomen (since the abdominal contents can be in the thorax), diminished breath sounds ipsilateral to the side of the hernia, and displacement of the heart sounds contralateral to the hernia. A chest x-ray can confirm the diagnosis if bowel gas is visible above the diaphragm accompanied by a mediastinal shift. Congenital diaphragmatic hernia can be detected prenatally by an ultrasound examination performed during the second trimester in most affected infants.

Management. Newborns with CDH are intubated immediately to avoid bag-mask ventilation and inflation of the bowel that has herniated into the chest; care is taken to minimize barotraumas induced by positive pressure ventilation. Correction of hypercapnea and pre-ductal hypoxemia are focused on assuring adequate end organ perfusion. Infants with CDH are treated with minimal sedation and pressure support modes of ventilation; some centers use high-frequency oscillatory ventilation (HFOV). Extra-corporeal membrane oxygenation (ECMO) is used in some centers for neonates with critical cardiopulmonary deterioration. The ex-utero intrapartum treatment (EXIT) procedure transitions a newborn directly onto

cardiopulmonary bypass when oxygenation and ventilation by intubation and mechanical ventilation are not expected to be possible. Other therapies that have been introduced in the acute neonatal treatment phase for CDH include nitric oxide (NO), delay of surgical repair, and use of surfactant and perflubron. Fetal surgery is possible for severely affected infants. Long-term follow-up for infants with CDH is provided at specialized centers.

Genetic counseling. CDH occurs as an isolated finding, as part of a genetic syndrome or chromosome abnormality, or as part of a complex but nonsyndromic set of findings. Kindreds representing both syndromic and nonsyndromic CDH consistent with autosomal dominant, autosomal recessive, and X-linked patterns of inheritance have been reported and some pedigrees suggest incomplete penetrance. The recurrence risk in subsequent pregnancies depends on whether the CDH is isolated, complex but nonsyndromic, or caused by a genetic syndrome or chromosome abnormality. Sibling recurrence for isolated Bochdalek hernia, the most common type of defect, is generally low (~1-2%); however, pedigrees consistent with monogenic inheritance have been reported. Prenatal diagnosis is possible by ultrasound examination. MRI is especially useful for the prenatal diagnosis of thoracic lesions that are atypical or complicated by multiple abnormalities and for assessing lung volumes.

Definition

The diaphragm is the structure that separates the thoracic and abdominal cavities to maintain the pressure differentials of the respective compartments.

Congenital diaphragmatic hernia (CDH) refers to a developmental defect of the formation of the diaphragm that, in most cases, is evident at birth. Although CDH is classified into several types, distinction among hernias can be problematic. An anatomic depiction of the normal diaphragm is presented in Figure 1 and anatomic descriptions of diaphragmatic defects are presented in Figure 2.

Posterolateral (Bochdalek) hernia. This posterolateral defect in the diaphragm, commonly referred to as a Bochdalek hernia, is often accompanied by herniation of the stomach, intestines, liver, and/or spleen into the chest cavity. An extremely large defect, or apparent absence of the hemidiaphragm, is called agenesis of the diaphragm; this defect probably represents the severe end of the Bochdalek hernia spectrum rather than a distinct entity.

Posterolateral hernias comprise approximately 80-90% of all CDH and appear to fall into two types: a) a diaphragmatic defect accompanied by absent or extremely deficient rim of posterior and lateral musculature (see Figure 2a); and b) a diaphragmatic defect with an intact rim of posterior and lateral musculature.

About 85% of Bochdalek hernias occur on the left side, about 10% on the right, and approximately 5% are bilateral.

Non-posterolateral (non-Bochdalek) hernia. Anterior defects of the diaphragm can occur in the midline, on the left side, or the right side. Several distinct "sub-types" are described, but considerable overlap in the anatomic location among these defects exists. Furthermore, it is not clear whether these "sub-types" share a common embryological mechanism.

a **Morgagni (Morgagni-Larrey) hernia.** Morgagni hernia is an anterior retrosternal or parasternal hernia that can result in the herniation of liver or intestines into the chest cavity (see Figure 2b). Morgagni hernias comprise approximately 2% of all CDH, are generally accompanied by a hernia sac, and often do not cause symptoms in the newborn period.

b **Other anterior hernias associated with Pentalogy of Cantrell.** These rare and severe types of hernias, possibly derived from the septum transversum, are found in individuals with Pentalogy of Cantrell (which also includes defects in the supraumbilical midline abdominal wall, lower sternum, diaphragmatic pericardium, and heart).

c **Central hernia.** This hernia is a rare diaphragm defect involving the central tendinous (e.g., amuscular) portion of the diaphragm. The entire rim of diaphragmatic musculature is present (see Figure 2c). Whether abnormal septum transversum development results in central as well as more anteriorly located hernias, and also whether central hernias can be distinguished from posterolateral hernias with a complete rim of musculature, is still a matter of debate.

Diaphragmatic eventration. Diaphragmatic eventration is incomplete muscularization of the diaphragm resulting in a thin membranous sheet of tissue. It is difficult to estimate the frequency of eventration because it may co-exist with a Bochdalek hernia with which it is often clinically misdiagnosed. Severe diaphragmatic eventration is associated with pulmonary hypoplasia and respiratory distress during infancy. Milder degrees of diaphragmatic eventration can present later in life with respiratory symptoms such cough and pneumonias or without symptoms so that the diagnosis is made incidentally on chest x-ray. Increasingly, it is observed that eventration of the diaphragm and "true" CDH can occur in the same individual, suggesting that in some instances they share a common etiology.

All hernia types can present with a sac (e.g., membranous sheet of tissue) covering the herniated abdominal contents. There currently is no explanation for the development of a hernia sac; however, its presence portends a better prognosis. Because a thin and redundant membranous diaphragm resulting from an eventration defect may represent a "sac," it is probable that eventration and "sac type" CDH diagnoses are often interchanged.

Embryology. Development of the diaphragm takes place between the fourth and twelfth weeks of pregnancy. The normal development of the diaphragm is not well understood. The diaphragm forms as a membranous sheet that most likely arises from different components:

- **The central portion and possibly anterior regions of the diaphragm** are thought to develop from the septum transversum, which is initially fused to the liver during development and becomes the unmuscularized central tendon of the diaphragm [Yuan et al 2003]. The contribution to the mature diaphragm from the septum transversum remains poorly understood.
- **The posterolateral section of the diaphragm** , the region that is deficient in the Bochdalek hernia, is thought to develop, in part, from the pleuroperitoneal folds (PPFs), triangular structures derived from mesoderm that develop in the thorax during early diaphragmatic development. These PPFs are thought to contribute to the connective tissue portion of the diaphragm. The membranous diaphragm is subsequently muscularized by muscle precursor cells that migrate first to the PPF from the cervical somites before proliferating, differentiating, and migrating onto the membranous diaphragm [Birchmeier & Brohmann 2000, Babiuk & Greer 2002, Babiuk et al 2003]. It is believed that a Bochdalek hernia forms if the PPFs do not fuse with the septum transversum and the dorsal mesentery of the esophagus by the tenth week of gestation
- **Co-existing pulmonary abnormalities.** The pathogenesis of the pulmonary hypoplasia so frequently associated with CDH is not fully known, but appears to have both a primary component, i.e., the hypoplasia occurs along with the diaphragm defect, and a secondary component, i.e., arising from competition for thoracic space

particularly in the lung ipsilateral to the hernia. Differing degrees of bilateral pulmonary hypoplasia may explain the variance in severity seen among neonates presenting with respiratory distress and CDH. This is supported by the nitrofen and *Fog2* animal models (described below) in which both primary pulmonary hypoplasia and diaphragmatic defects are observed [Guilbert et al 2000,Ackerman et al 2005].

Abnormal pulmonary vascular development and function is a significant problem in infants with CDH. The mechanism of pulmonary hypertension in CDH is not completely understood. The size of the pulmonary vascular bed is decreased in the hypoplastic lungs, and the adventitia and media of the pulmonary arterial walls are thickened [Yamataka & Puri 1997]. These changes occur in utero and are more severe in term neonates than in pre-term neonates.

Clinical Manifestations

Infants with CDH often present in the neonatal period with severe respiratory distress. Breath sounds are diminished ipsilateral to the hernia and heart sounds are evident contralateral to the hernia. Combining all hernia types, CDH occurs 80-90% of the time on the left side, 10-20% on the right side, and less than 5% of the time bilaterally [Torfs et al 1992, Dott et al 2003].

Five to ten percent of individuals with CDH, even those with a Bochdalek hernia, do not show symptoms in the newborn period. Presenting symptoms after infancy can be acute onset of respiratory or gastrointestinal distress, or low-grade symptoms such as abdominal pain from chronic intestinal obstruction or pleural effusion from entrapment of the bowel in the chest. About 1% of individuals are completely asymptomatic and the defect is discovered incidentally on imaging studies [Baglaj & Dorobisz 2005].

Establishing the Diagnosis

Over 50% of cases with CDH are detected prenatally by ultrasound examination. MRI is especially useful for the prenatal diagnosis of thoracic lesions that are atypical or complicated by multiple abnormalities and for assessing lung volumes [Hubbard et al 1997, Matsuoka et al 2003]

In the newborn, the abdomen is scaphoid; chest x-ray confirms the diagnosis of CHD when bowel gas visible above the diaphragm is accompanied by a mediastinal shift.

Differential Diagnosis

Bronchogenic (foregut duplication) cysts. Bronchogenic cysts result from abnormal budding of the ventral foregut [Knudtson et al 2004]. They contain several components of the bronchi, including respiratory epithelia, mucous glands, and cartilage and may occur anywhere along the length of the trachea or esophagus. Most are diagnosed incidentally, although cysts can become infected or if large enough, can compress the esophagus and/or trachea.

Congenital cystic adenomatoid malformation (CCAM). CCAM is a developmental abnormality of the lung resulting from abnormal cell proliferation and decreased programmed cell death of lung tissue. Abnormally formed bronchi connect to the CCAM. Type I CCAM is most common and is distinguished by relatively large cysts and mucin production. Symptoms can result when CCAMs grow in size and compress structures in the mediastinum.

Cystic teratoma. Cystic teratomas are benign tumors most often found in the anterior mediastinum [Jaggers & Balsara 2004]. They consist of several differentiated cell types derived from endoderm, ectoderm, and/or mesoderm. Cystic teratomas of the mediastinum are uncommon, comprising fewer than 10% of all tumors in that region.

Neurogenic tumors. These are the most common lesion found in the posterior mediastinum. They are likely to be of neural crest origin; the majority are benign. Examples include: neurilemmoma, neurofibroma, ganglioneuroma, pheochromocytoma, and neuroblastoma. CT and MRI are helpful in establishing the diagnosis.

Paraesophogeal hernia. This hernia occurs when a portion of the stomach and sometimes part of the peritoneal sac containing the spleen or colon move into the chest cavity through the normally occurring, but generally enlarged or dilated, esophageal hiatus. More accurately, paraesophageal hernias are a type of hiatal hernia, in which the stomach gets "stuck" in the chest, rather than sliding back and forth between the thorax and abdomen. Approximately five to ten percent of (acquired) hernias are paraesophageal. They are rare in infancy and most commonly present in older adults.

Pulmonary agenesis. Partial or complete absence of lung tissue that is caused by failure of lung bud development is termed pulmonary agenesis. It is often associated with additional congenital malformations.

Pulmonary sequestration. Primitive lung tissue that is not connected to the tracheobronchial tree results in pulmonary sequestration. Sequestration may be intrapulmonary, occurring within the pleura of the normal lung, or extrapulmonary, occurring outside the normal lung within its own pleural sac. Extrapulmonary sequestration seems to arise from an accessory lung bud and often has associated anomalies, such as CDH. The most common presenting symptom is respiratory, such as recurrent chest infections. MRI can accurately distinguish between pulmonary sequestration and CCAM [Quinn et al 1998].

Although all of the above lesions can remain undetected, respiratory symptoms usually develop at some point. Bronchogenic cysts, CCAM, and pulmonary sequestration should be surgically resected within the first few months of life to maximize growth of the surrounding normal lung tissue [Laberge et al 2005].

Prevalence

The prevalence rate for all types of CDH is approximately one in 3000 live births, although considerable variation has been reported with frequencies as low as one in 5,000 [Philip et al 1991, Langham et al 1996]. The disparity in prevalence may be attributable to varying study methodologies such as different inclusion criteria and modes of ascertaining affected individuals.

Lower prevalence rates may be seen in studies in which CDH is not diagnosed in pregnancy terminations, stillborn fetuses, neonatal deaths, or in which cases diagnosed after infancy escape ascertainment [Langham et al 1996]. It has been reported that as many as 13% of CDH cases are undiagnosed in early infancy [Nitecki & Bar-Maor 1992]. Higher prevalence rates may be seen in studies that have fuller ascertainment including a greater number of prenatally diagnosed cases [Skari et al 2002] or that examine a geographically defined population with a thorough review of all postmortem cases, including those with unexplained respiratory distress.

No significant variation in geographic region or ethnicity has been identified [Torfs et al 1992, Robert et al 1997]. Some, but not all, studies have found more affected males than females with CDH. It is difficult to resolve these discrepancies, although they may be the result of differing study demographics, such as the distribution of isolated CDH, in which no other malformations are present, versus complex CDH, in which other malformations are observed. No evidence associates CDH with advanced maternal age, but data from one study suggest that advanced parental age may be a risk factor [McIntosh et al 1995].

Mortality. Mortality from CDH continues to be high, ranging from 20% to 60%. Data from neonatal or referral centers operating on relatively selected cases, primarily those with isolated left-sided Bochdalek hernia, report 80-90% survival [Downard et al 2003]. However, population-based studies of outcome for all prenatally diagnosed CDH cases report mortality of at least 50%, if pregnancy terminations are included [Colvin et al 2005]. In a meta-analysis, Stege et al (2003) observed that approximately one-quarter of all prenatally diagnosed cases were electively terminated, three percent spontaneously miscarried, and three percent were stillborn; 31% of the liveborns died, the majority within the first 24 hours of life.

The key determinants of mortality:

- Whether the CDH is isolated or complex. Higher mortality occurs with complex CDH associated with a chromosome abnormality, a single gene disorder, and/or the co-existence of major malformations. The presence of a cardiovascular malformation also indicates a worse prognosis [Cohen et al 2002].
- The degree of pulmonary hypoplasia
- Whether the liver is up in the chest or remains down below the diaphragm [Albanese et al 1998]. Individuals with a large amount of "liver up" CDH have higher mortality compared to those whose livers remain down below the diaphragm.
- The severity of pulmonary hypertension in the perinatal period. Pulmonary hypertension, which may progress to a late or chronic phase, is often not responsive to medical therapy [Kinsella et al 2005]
- Whether the hernia is right-sided, left-sided, or bilateral. Some, but not all, studies show that a right-sided hernia is associated with greater mortality than a left-sided hernia [Skari et al 2000]. Bilateral CDH always confers a very high mortality.

Morbidity. Multi-organ morbidity is considerable among survivors, even those with seemingly isolated CDH. For many survivors, CDH is truly a chronic disease, although reports of essentially normal, or near normal, long-term outcomes are increasing. It can be difficult to determine whether certain abnormalities are intrinsic to the condition or secondary to treatment. The most vulnerable organ systems include the following:

- **Pulmonary.** Almost all individuals with CDH have some degree of pulmonary hypoplasia. Many infants require oxygen supplementation and diuretics following surgical correction of CDH. Given the remarkable growth and recuperative capacity of the lung, these treatments can usually be discontinued within the first two years of life. However, limited pulmonary reserve secondary to pulmonary hypoplasia persists and respiratory decompensation often occurs with intercurrent illness. Reactive airway disease is also common in young children. Clinical evidence of respiratory symptoms when the individual is at rest resolves over time, but formal testing even in older children shows small airway obstruction and diminished blood flow on ventilation-perfusion (V-Q) scan, especially to the lung ipsilateral to the hernia. Limited exercise tolerance can be a lifelong problem.
- **Gastrointestinal.** "Failure to thrive" with growth parameters less than the third centile of normal is common among infants with more significant pulmonary hypoplasia and/or a more prolonged hospitalization following surgical repair of CDH. Growth failure is caused, in large part, by oral aversion and feeding difficulties (often requiring gastrostomy tube insertion for the first few years of life) and gastroesophageal reflux (frequently requiring pharmacotherapy and/or surgical fundoplication). Some infants and children require long-term high calorie nutritional supplements.

- **Neurologic/developmental.** In early reports of long-term survivors, neurological abnormalities and mild-to-moderate developmental delay were common, especially among those receiving ECMO (extra-corporeal membrane oxygenation) treatment [Lund et al 1994]. Information about developmental outcomes using more current practice standards is limited by lack of prospective studies testing with standard developmental assessment tools. However, it appears that most children who are not diagnosed with a chromosome abnormality or syndrome have full-scale IQ scores in the low-average or average range, with virtually none being mentally retarded (i.e., IQ score <70) [Bouman et al 2000; S Freedman, personal communication]. Children with normal IQs remain vulnerable to learning and attention problems. Non-focal neurological abnormalities such as hypotonia are common. Nonspecific findings such as cortical atrophy and ventriculomegaly can be seen on neuroimaging studies [Ahmad et al 1999, Bouman et al 2000, Rasheed et al 2001].
- **Musculoskeletal.** Chest asymmetry is found in as many as half of individuals with CDH. Pectus, most often of the excavatum type, and scoliosis (≥10°f Cobb's angle) are found in approximately 25% of individuals [Vanamo et al 1996]. These musculoskeletal abnormalities occur more often following repair of large diaphragmatic defects, possibly as a result of the extra tension exerted on the chest wall during surgical repair.
- **Hearing loss.** Sensorineural hearing loss (SNHL) has been found in 25% of individuals with CDH and as many as 100% of individuals treated with ECMO in some series [Rasheed et al 2001, Robertson et al 2002]. One study of ECMO survivors showed that SNHL, often of delayed onset, was 2.5 times more common among those requiring ECMO for CDH than for other indications. Prolonged treatment with aminoglycosides and ECMO increased the risk for SNHL, independent of the indication for the use of ECMO. Among this cohort, 60% of the CDH survivors had SNHL that was often severe. Other factors such as use of nitric oxide, prolonged or high-frequency mechanical ventilation, and/or metabolic alkalosis might also contribute to the development of SNHL [Fligor et al 2005].
- **Reherniation.** At least ten percent of individuals reherniate. The risk for this is considerably greater among those whose hernia repair required a prosthestic patch.

Causes

Environmental Causes

No confirmed cases of CDH in humans have been attributed to teratogenic or environmental exposures. However, CDH can be produced in experimental animals and the two best-studied models are described in Animal Models of CDH.

Heritable Causes

Chromosomal Abnormalities—About 10% of all individuals with CDH have a chromosome abnormality. The most common abnormalities are trisomy 18 and isochromosome 12p (Pallister-Killian syndrome or PKS), although many additional abnormalities have been reported (Table 1). Several small rearrangements have been found in unrelated individuals, suggesting that one or more genes important for normal diaphragm development reside in these critical regions. The best characterized of these regions is 15q26.2; currently, several candidate genes are being sequenced to determine whether or not they play a causal role in human CDH. Other apparent chromosome "hotspots" for CDH include: 1(q41-q42), 8q22.3 (the *FOG2* locus), and possibly (22)(q11-qter).

Isochromosome 12p (tetrasomy 12p; Pallister-Killian syndrome). The presence of a supernumerary isochromosome, consisting of two copies of the short arm of chromosome 12, confirms the diagnosis of PKS. Affected individuals have four copies of the genes on chromosome 12 p: two copies from the pair of normal chromosomes 12 and two additional copies from the supernumerary chromosome. Mosaicism for the isochromosome is a cardinal finding in the disorder. Specifically, the isochromosome is rarely found on standard blood (lymphocyte) chromosome analysis, but can be documented in five to 100% of amniocytes, chorionic villi, and skin fibroblasts [Doray et al 2002]. The isochromosome generally results from a maternal premeiotic or meiotic error accompanied by centromere misdivision; it is more commonly found in offspring of mothers over 35 years of age (advanced maternal age). In the setting of CDH, chromosome 12p FISH is increasingly being used as an adjunct to standard karyotyping and may identify additional PKS cases caused by low-level mosaicism.

The spectrum of clinical problems in PKS ranges from multiple malformations incompatible with life to milder phenotypes with few medical and developmental abnormalities. The explanation for this variability is not known, but may be partly attributed to tissue mosaicism. The abnormalities most frequently seen on prenatal ultrasound examination include CDH, relatively shortened limbs, CNS anomalies and ventricular dilatation, craniofacial dysmorphology, and evidence of excess fluid accumulation, such as nuchal edema and/or hydrops fetalis [Doray et al 2002]. Polyhydramnios commonly accompanies PKS, but is not specific for the disorder.

Prominent clinical features identified post-natally are bi-temporal sparseness of hair, facial dysmorphology (brachycephaly, high broad forehead, hypertelorism, low-set ears, broad nasal bridge, anteverted nostrils, long philtrum) that progressively coarsens over time, short neck with nuchal skin redundancy, short broad hands, linear streaks of skin hyperpigmentation, and normal growth. Seizures commonly develop during infancy. Most individuals demonstrate at least moderate mental retardation, although some have only mild developmental problems. It is possible that PKS is even more common than currently appreciated, since skin chromosome analysis is not always performed on mildly affected individuals.

It is important to distinguish PKS from Fryns syndrome as the former is not hereditary, while the etiology of the latter has been attributed to autosomal recessive inheritance. The considerable phenotypic overlap between both disorders includes CDH, "coarse facies," and minor limb anomalies. Nail hypoplasia, one of the hallmarks of Fryns syndrome, has been reported in a few individuals with PKS. Features that are more common in, but not pathognomonic for, Fryns syndrome include CDH, cleft palate, distal phalangeal and/or nail hypoplasia, cardiovascular malformations, and renal malformations. Features more common in PKS include a high forehead, streaky skin hyperpigmentation, and sparseness of hair bi-temporally [McPherson et al 1993].

Trisomy 18. Trisomy 18 is the second most common autosomal trisomy, after trisomy 21, identified in infants with multiple anomalies who survive to the perinatal period. The most salient features are intrauterine growth retardation, cardiovascular malformations, craniofacial dysmorphology, and characteristically clenched hands [Tongsong et al 2002]. A broad array of other major malformations can occur. The frequency of CDH in trisomy 18 is not known, but could be as high as one to two percent as it is the most commonly detected chromosome abnormality in all prenatal series of CDH cases. Trisomy 18 mortality is extremely high with few long-term survivors.

Trisomy 21. Although infants with trisomy 21 can have either Bochdalek or Morgagni hernia, the overall frequency of CDH in trisomy 21 seems to be low. Morgagni hernias are more

commonly reported than Bochdalek hernias, suggesting it is the most common type of CDH among individuals with trisomy 21 [Torfs et al 1992].

Del (4)(p16) (Wolf-Hirschhorn syndrome, WHS). WHS is characterized by typical craniofacial features, prenatal-onset and postnatal growth deficiency, and developmental delay/mental retardation. Individuals with Wolf-Hirschhorn syndrome have a deletion in the distal portion of the short arm of chromosome 4 involving band 4p16 (loosely termed 4p-). It seems likely that a gene important for diaphragm development is deleted in at least some individuals with Wolf-Hirschhorn syndrome, as there are several case reports of CDH in persons with 4p- [Sergi et al 1998, van Dooren et al 2004]. However, no genotype-phenotype correlations can yet be made as variable-sized deletions occur in association with CDH.

+der (22) t(11;22)(q23;q11) and trisomy 22. In addition to reports of persons with +der (22), some individuals with trisomy 22 have CDH, suggesting that three copies of a gene (or genes) on 22q contribute to CDH. Individuals trisomic for 22q11' 22qter commonly have growth retardation, mental retardation, cardiovascular malformations, craniofacial anomalies (including preauricular tags or sinuses, micrognathia, cleft palate), and abnormal ears.

del (15)(q26.2). CDH has been found in several unrelated individuals with a deletion of terminal 15q resulting from either an unbalanced translocation, a *de novo* deletion, or a ring chromosome. All have had mental retardation, growth retardation, and/or additional birth defects (craniofacial anomalies, cardiovascular malformations, hypoplastic genitalia, or cryptorchidism). Use of array-based comparative genomic hybridization (aCGH) and FISH has led to the identification of an ~5-Mb critical region in 15q26.2 that contains four known candidate genes for CDH: *NR2F2 (COUPTFII*; a steroid receptor involved in the retinoic acid pathway that binds *FOG2*), *CHD2* (a chromodomain helicase), and *RGMA* and *SIAT8B* (two neural migration molecules) [Klaassens et al 2005]. Array-based CGH has also identified del (15)(q26.2) in two individuals with CDH plus additional malformations in individuals who had prior normal routine karyotypes [Slavotinek et al 2005].

del (1)(q41-q42). Use of array-based comparative genomic hybridization (CGH) demonstrated a deletion in chromosome (1)(q41-q42.12) in an individual with Fryns syndrome [Kantarci et al 2006]. This finding, in conjunction with previous reports of cytogenetic abnormalities in multiply malformed infants with CDH [Youssoufian et al 1988, Smith et al 1994, Rogers et al 1995] suggests that the locus contains a gene important for diaphragm development.

del (8)(p23.1). These individuals have cardiovascular malformations, mental retardation, mild facial dysmorphology, and renal anomalies.

Table 1. Common Chromosomal Anomalies Associated with CDH

Chromosome Abnormality / Locus	Frequency of Congenital Diaphramatic Hernia [1]	
	Found in this Disorder	Attributed to this Disorder
Pallister-Killian syndrome / (isochromosome or tetrasomy 12p)	~30%	?<5%
Trisomy 13	Rare	Very rare
Trisomy 18	?1-2%	Rare among all CDH; most common chromosome abnormality in prenatally diagnosed CDH
Trisomy 21	Rare	Very rare
Del (4)(p16) (Wolf-Hirschhorn syndrome)	Rare	Very rare
+der (22) t(11;22)(q23;q11)	5-10%	Very rare
Del (15)(q26.2)	Unknown (?but possibly majority)	Unknown [2]
Del (1)(q41-q42)	Unknown	Unknown [2]
Del (8)(p23.1)	~15%	Unknown [2]

For a more detailed discussion of chromosome abnormalities and CDH, see Lurie (2003)

1. Authors' estimate of frequency

2. Small chromosome deletions of these regions, or point mutations of genes mapping to these regions, may cause CDH. The frequency with which these occur is presently unknown.

Single Gene Disorders—Some of the more common monogenic syndromes in which CDH occurs are listed in Table 2; a few of these syndromes are presented in greater detail below.

Cornelia de Lange syndrome (CdLS). CdLS is characterized by distinctive facial features (synophrys, arched eyebrows, long eyelashes, small upturned nose, small widely spaced teeth), microcephaly, growth retardation (prenatal onset and below the fifth centile throughout life), hirsutism, and upper limb reduction defects that range from subtle phalangeal abnormalities to oligodactyly [Opitz 1985]. The frequency of CDH in CdLS is not precisely known but may be as high as 5%. Prenatal diagnosis of oligodactyly and CDH, especially in the presence of growth retardation, should prompt consideration of CdLS [Marino et al 2002]. The co-occurrence of more severe growth retardation and major malformations is associated with a worse neurodevelopmental outcome.

Mutations in *NIPBL* are identified in 50% of individuals with CdLS; molecular genetic testing is clinically available [Krantz et al 2004]. It is not known currently whether there is genetic heterogeneity in CdLS resulting from mutations in other genes or in regulatory genes for *NIPBL*. CdLS is inherited in an autosomal dominant manner with a *de novo* mutation responsible for the disorder in the vast majority of individuals.

Denys-Drash syndrome. This syndrome is a characteristic malformation complex consisting of genital anomalies, male pseudohermaphroditism, nephropathy (diffuse mesangial sclerosis), and an increased risk for Wilms tumor [Devriendt et al 1995, Devriendt et al 1996]. Missense mutations in the zinc-finger binding domains resulting in WT1 (-KTS*) are most commonly associated with Denys-Drash syndrome (see Wilms Tumor Overview).

*Splice variant in exon 9 with loss of lysine, threonine, and serine between third and fourth zinc finger

Donnai-Barrow syndrome (also known as diaphragmatic hernia, exomphalus, absent corpus callosum, hypertelorism, myopia, and sensorineural deafness syndrome) is a rare autosomal

recessive disorder in which a congenital diaphragmatic defect is found in approximately 50-70% of affected individuals. Common abnormalities include ocular hypertelorism, myopia, sensorineural hearing loss, omphalocele or umbilical hernia, enlarged anterior fontanel, agenesis of the corpus callosum, and mildly impaired cognitive development. The genetic basis of Donnai-Barrow syndrome is not known, but the disorder appears to be autosomal recessive based on reports of affected siblings and parental consanguinity [Donnai & Barrow 1993, Gripp et al 1997, Chassaing et al 2003].

Fryns syndrome. Fryns syndrome is a multiple malformation/mental retardation condition in which approximately 80% of individuals diagnosed with the syndrome have a congenital abnormality of the diaphragm, most commonly Bochdalek hernia. Additional features include a characteristic coarse facial appearance (often with widely spaced eyes, a broad nasal bridge, and macrostomia), hypoplasia of the nails and/or terminal phalanges, pulmonary hypoplasia, genitourinary anomalies (renal dysplasia and cysts, bicornuate uterus), ocular abnormalities (cloudy corneas), cardiovascular malformations, and orofacial clefting [Fryns et al 1979, Slavotinek 2004]. Lymphatic malformation resulting in cystic hygroma identified prenatally in some affected fetuses would account for the short broad neck observed postnatally in some infants [Van Wymersch et al 1996]. Polyhydramnios occurs in over 50% of pregnancies with Fryns syndrome. The prognosis is poor, with most affected infants succumbing soon after birth; a few long-term survivors demonstrate varying degrees of mental retardation [Van Hove et al 1995].

The genetic basis of Fryns syndrome is unknown, but has been considered to follow an autosomal recessive pattern of inheritance based on reports of sibling recurrences and parental consanguinity. However, *de novo* microdeletions at 1q41-q42 and 15q26.2 detected in some individuals with Fryns syndrome, or a Fryns-like phenotype, suggest that genetic heterogeneity may underlie this phenotype [Slavotinek et al 2005, Kantarci et al 2006]. Furthermore, since Fryns syndrome is a clinical diagnosis, it is possible that several distinct disorders with CDH are "lumped" under this designation. Diaphragmatic defects may not be as common in Fryns syndrome as currently estimated because the diagnosis is less likely to be entertained in the absence of CDH. Isochromosome 12p (Pallister-Killian syndrome) should be excluded by chromosome analysis or 12p FISH analysis prior to establishing the clinical diagnosis of Fryns syndrome.

Multiple vertebral segmentation defects (spondylocostal dyostosis, spondylothoracic dysostosis, Jarcho-Levin syndrome). Typical findings include hemivertebrae, vertebral fusion, scoliosis, rib anomalies, short stature, cleft palate, digital anomalies, and renal anomalies. More than half a dozen cases describing the co-occurrence of vertebral segmentation disorders with congenital defects of the diaphragm have been reported [Lam et al 1999, Day & Fryer 2003, Rodriguez et al 2004]. This suggests that mutations in the Notch signaling pathway or abnormal mechanical forces resulting from the complex spinal and rib defects increase the risk of CDH.

Simpson-Golabi-Behmel (SGB) syndrome. In this X-linked overgrowth syndrome, a minority of affected males have CDH. The most common physical finings are macrosomia, macroglossia, abdominal wall defects (including umbilical hernia and omphalocele), skeletal abnormalities (such as brachydactyly, postaxial polydactyly, cutaneous syndactyly), accessory nipples, coarse facial features, ocular hypertelorism, and renal anomalies (hydronephrosis, cystic dysplastic kidney) [Neri et al 1998]. Approximately half of affected infants die in the neonatal period, in some cases secondary to CDH. Males who survive long term typically have low normal intelligence, although a range of intellectual abilities has been reported. The risk for development of embryonal tumors is increased, but the magnitude of risk is not known; routine screening for Wilms tumor and hepatocellular carcinoma is indicated [Li et al 2001].

It can be difficult to distinguish Simpson-Golabi-Behmel syndrome from other overgrowth disorders, especially Beckwith-Wiedemann syndrome [Verloes et al 1995]. Most cases of SGB syndrome are caused by loss-of-function mutations in the gene encoding glypican 3.

Table 2. Selected Syndromes in Which CDH is a Feature

Syndrome	Mode of Inheritance	Gene Symbol	Chromosomal Locus	Frequence of CDH in this Disorder [1]
Cornelia de Lange syndrome	AD	*NIPBL* [2]	5p13.1	?up to 5%
Denys-Drash syndrome	AD	*WT1* (-KTS)	11p13	Rare%
Donnai-Barrow syndrome	AR	Unknown		~70%%
Fryns syndrome	Presumed to be AR, but phenotype recently reported in cases with *de novo* microdeletions	Unknown (possible etiologic heterogeneity)		>80% (but ascertainment may be biased)%
Multiple vertebral segmentation defects (spondylothoracic or spondylocostal) dysplasia, Jarcho-Levin syndrome)	Heterogeneous, including AR and AD	*DLL3*	19q13	Rare
		MESP2 [3]	15q26.1	
		LFNG [3]	7p22	
Simpson-Golabi-Behmel syndrome	X-Linked recessive	*GPC3*	Xq26	Rare

1. Author's estimate
2. *NIPBL* mutations in up to 50%
3. One family

Table 3. Selected Syndromes or Associations Which Less Frequently Have CDH as a Feature

Syndrome	Common Features	Inheritance Pattern	Gene Symbol (Chromosomal Locus)
Apert syndrome	Craniosynostosis, mid-face hypoplasia, hypertelorism, varying degrees of bilateral soft tissue and bony syndactyly of hands and feet, developmental delay/ mental retardation in ~50%, fusion of cervical vertebrae	AD (most cases new dominant mutations)	*FGFR2* (10q26)
Beckwith- Wiedemann syndrome	Prenatal and/or postnatal overgrowth, macroglossia, abdominal wall defects, earlobe creases or pits behind the upper ear, visceromegaly, hemihypertrophy, embryonal tumors	Majority of cases are "sporadic" but can be transmitted as AD, especially if mother carries *CDKN 1C* mutation	Dysregulation of imprinted genes on 11p15.5
CHARGE syndrome	Coloboma, CVMs, choanal atresia or stenosis, genital anomalies, ear anomalies	AD (all cases reported to date new dominant mutations)	*CHD7* (8q12.1)
C Trigonocephaly syndrome	Trigonocephaly caused by metopic craniosynostosis, orofacial anomalies (deep midline palatal groove, broad alveolar ridges, multiple frenula). Associated with various renal, pulmonary, genital, and cardiovascular defects. Short limbs and polydactyly can occur. Loose skin, mental retardation common but not obligatory.	?AR or ?microdeletion syndrome	Unknown

Coffin-Siris syndrome	Hypoplasia / absence of nail/phalanx of fifth digit (and occasionally of additional digits), scalp hypotrichosis, body hypertrichosis, facial dysmorphology (coarse face, wide mouth, full lips), growth retardation, mental retardation. Additional major malformations of the heart and brain can occur. Female:male ratio ~4:1. May be difficult to distinguish from Fryns syndrome.	?AR	Unknown
Craniofrontonasal syndrome	Hypertelorism, broad/bifid nasal tip, coronal craniosynostosis, grooved nails of hallux and thumb, mild cutaneous syndactyly, mild skeletal abnormalities. Males less severely affected than females.	X-linked	*EFNB1* (Xq12)
Czeizel-Losonci syndrome	Limb anomalies (split hand/split foot, preaxial deficiency, syndactyly), urinary tract obstruction, neural tube defects, ?TE-fistula, ?deficient skull ossification	AD	Unknown
Gershoni-Baruch syndrome	Omphalocele, CVMs, absent radial ray, vertebral anomalies, neural tube defect, perinatal lethal	AR	Unknown
Goltz-Gorlin syndrome (focal dermal hypoplasia)	Asymmetry of the face, trunk, and extremities; skin atrophy following lines of Blaschko, subcutaneous nodules secondary to fat herniation through atrophic areas; alternating areas of hyper- and hypopigmentation following lines of Blaschko, multiple mucous and perioral papillomas; skeletal abnormalities involving the extremities (syndactyly, polydactyly, absent digits). Hypoplasia or aplasia of teeth, enamel defects, malocclusion. Coloboma, micro-ophthalmia. Osteopathia striata (radio-opaque striations of long bones). Mild mental deficiency. High frequency of male lethality	X-linked dominant	Unknown
Kabuki syndrome	Distinctive face (long palpebral fissures, eversion of lower eyelids, arched/discontinuous eyebrows with lateral thinning). Prominent ears. Fetal finger pads. Short fifth finger. High arched palate (occasional cleft lip ± palate). Postnatal growth deficiency, mild-to-moderate mental retardation. CVMs. Hypotonia	?AD	?dup (8)(p22p23.1) [1]
Marfan syndrome	Connective tissue dysplasia characterized by tall stature (compared to unaffected family members), disproportionately long extremities, subluxation of the lens, dilatation of the ascending aorta. Diaphragmatic defects are rare but among those that occur, eventration is more common than an actual hernia ("hole").	AD	*FBN1* (15q21.1)
Mathieu syndrome	Facial dysmorphology (epicanthal folds, short nose, depressed nasal bridge, micrognathia), cleft palate, short stature, short neck, vertebral anomalies, mild mental retardation, and tracheal anomalies	AD	Unknown

Meacham syndrome	46,XY males, undervirilization of external male genitalia ↓ambiguous or female external genitalia, retained Mullerian structures with double vagina, pulmonary hypoplasia, and possible abnormal differentiation of the lung, complex CVMs	AD (presumably new dominant mutations)	*WT1* (11p13) (mutation identified in one case to date)
Matthew-Wood syndrome	Pulmonary hypoplasia / aplasia. Anophthalmia / microphthalmia, CVMs. Prenatal growth retardation. Similar cases have been designated as PMD syndrome (**p**ulmonary agenesis, **m**icrophthalmia, & **d**iaphragmatic defect).	AR	Unknown
MIDAS syndrome	Microphthalmia, sclerocornea, linear dermal hypoplasia, occasional CVMs and genital anomalies	X-linked	*MLS* (Xp22.3)
PAGOD syndrome	Pulmonary hypoplasia, hypoplasia of the pulmonary artery, agonadism, omphalocele, diaphragmatic defect, and dextrocardia. Gonads may be small rather than absent and ambiguous genitalia can occur. CVMs and great vessel abnormalities are common.	?AR (??defect in vitamin A pathway)	Unknown
Pentalogy of Cantrell	Deficiency of anterior diaphragm, defect of diaphragmatic pericardium, ectopia cordis or other CVMS, supraumbilical abdominal wall defect, defect of lower sternum. Definitive diagnosis is made when 5/5 abnormalities are present, probable cases have 4/5 defects (but always CVMs, sternal and abdominal wall defects), and possible cases have 3/5 (but always the sternal defect)	Sporadic/Random	Unknown
Perlman syndrome	Macrosomia, nephromegaly, (with renal hamartomas, most often nephroblastosis), hydronephrosis, increased risk for Wilms tumor, hepatomegaly, hyperplasia of the endocrine pancreas, typical facial appearance, high neonatal lethality, mental retardation in survivors	?AR	Unknown (?locus on 11p)
Poland anomaly	Unilateral symbrachydactyly, ipsilateral aplasia of the sternal head of the pectoralis major muscle	Sporadic	Unknown
Swyer syndrome	46, XY sex reversal, partial or complete gonadal dysgenesis	Heterogeneous causes (~30% of Swyer syndrome cases caused by mutation or deletion of *SRY*; however, no *SRY* mutations have been documented to date in persons with Swyer syndrome and CDH)	Unknown
Thoraco-abdominal schisis	Abdominal wall defect (absent or hypoplastic abdominis rectus muscle), anterior diaphragm defect, hypoplastic lung, occasional CVMs, cleft palate Males affected more severely than females. ?Represents fusion-schisis abnormality. Phenotype can be similar to Limb-Body Wall (LBW) complex but the abdominal wall defect in LBW is not midline.	?X-linked	Unknown

Table **does not** include single case reports of CDH.

1. Duplication by CGH reported in some cases but not confirmed in others

Malformations Commonly Associated with Nonsyndromic Complex CDH —At least one-third of infants with CDH have additional major malformations that do not occur as part of a currently recognized monogenic syndrome or chromosome abnormality. The most common associated malformations are those involving the cardiovascular, central nervous, musculoskeletal, and genitourinary systems. It is difficult to know the exact frequency with which these malformations occur in nonsyndromic CDH, as many studies tabulate syndromic and nonsyndromic cases together.

In the future, some cases currently classified as complex nonsyndromic CDH are likely to be reclassified as having single gene disorders or microdeletion chromosome abnormalities.

CDH and cardiovascular malformations. Cardiovascular malformations (CVMs) are common in individuals with CDH. In several population based surveys, approximately 10-15% of all infants with nonsyndromic CDH had an accompanying CVM [Philip et al 1991, Robert et al 1997, Dillon et al 2000, Dott et al 2003, Tonks et al 2004]. In a large autopsy series, 24% of infants with CDH had a CVM; however, cases with chromosome abnormalities and known syndromes were not excluded [Migliazza et al 1999]. Several other series report 25-50% frequency of associated CVMs but also include syndromic cases.

No type of CVM is over-represented in nonsyndromic CDH. The most common malformations are a ventricular septal defect (VSD) or an atrial septal defect (ASD), although conotruncal defects, such as tetralogy of Fallot are seen as well. A small left heart, sometimes called hypoplastic left heart syndrome, is sometimes "diagnosed" in individuals with left-sided CDH. Careful scrutiny of the cardiac findings in these individuals often does not support a diagnosis of complete or full hypoplastic left heart syndrome; rather the left heart structures are small, possibly due to abnormal hemodynamics in the setting of a left-sided diaphragm defect. The mediastinal shift created by a left-sided CDH can lead to apparent dextrocardia, when in fact the altered position is dextroposition (e.g., the heart is shifted into the right chest).

CDH and central nervous system abnormalities. CNS anomalies co-exist in up to ten percent of nonsyndromic CDH cases; the most common diagnoses are neural tube defects and hydrocephalus [David & Illingworth 1976, Dillon et al 2000, Dott et al 2003]. The reason for the common association with a neural tube defect is not known, but has been postulated to be a problem of schisis-fusion or midline instability [Czeizel et al 1981, Opitz 1982].

Abnormalities on neuroimaging, such as frontal atrophy and/or ventriculomegaly are often seen following repair of CDH; these findings probably do not represent malformations of the CNS, but rather sequelae of treatment.

CDH and limb abnormalities. Limb defects, including absence defects, polydactyly, and syndactyly, are found in approximately ten percent of nonsyndromic CDH [Torfs et al 1992, van Dooren et al 2003]. The greatest attention has been paid to limb reduction defects present in approximately two percent of individuals with nonsyndromic CDH. The range of defects is broad, from hypoplastic thumb to Poland anomaly to phocomelia [Lerone et al 1992, Hou & Wang 1999]. McCredie and Reid (1978) speculated that disturbed migration of cervical neural crest cells accounted for both problems; however, a unifying mechanism has not been proven. Perhaps a gene important for limb and diaphragm (and pulmonary) development, such as *FGF10*, is mutated in some of these individuals [van Dooren et al 2003].

CDH and genitourinary abnormalities. Undescended testes commonly co-exist with CDH [Lund et al 1994]; ectopic or absent testes are also reported. A rarer finding includes ectopic (thoracic) kidney [Masturzo et al 2001]. In one series, a high percentage of individuals with nonsyndromic CDH and limb reduction defects had renal agenesis, horseshoe kidney, or ectopic kidney [van Dooren et al 2003]. Although this section focuses on the non-random

clustering of malformations that occur outside of well-defined syndromes, it is important to note that several syndromes in Table 3 (Meacham syndrome, Swyer syndrome, PAGOD syndrome) can have CDH in association with gonadal aplasia/hypoplasia plus ambiguous genitalia or complete sex reversal. Whether these historically distinct syndromes share a common genetic etiology is currently unknown.

CDH and eye abnormalities. Eye abnormalities, notably microphthalmia and anophthalmia (see Anophthalmia/Microphthalmia Overview) are reported in several syndromes listed in Table 3 (Matthew Wood/PMD syndrome, Goltz-Gorlin syndrome, Fryns syndrome). The co-occurrence of these rare malformations is likely not random and reflects either pleiotropic manifestations of an underlying genetic disorder, a developmental field defect [Steiner et al 2002], or possibly vitamin A deficiency [Macayran et al 2002].

Unknown Causes

Currently, about 15-20% of individuals with CDH have an identifiable cause for their diaphragm defect [Pober et al 2005]. These individuals are classified as having syndromic CDH either resulting from a recognized chromosome abnormality or a single gene disorder. In the remaining 80-85% of individuals with CDH, the etiology is not known and is likely caused by: (1) an unknown (and therefore undetectable) small genomic microdeletion or microduplication; (2) a mutation in a major gene important for diaphragm development; (3) the combinatorial effects of multiple minor genetic mutations or variants (so-called polygenic inheritance); or (4) the effects of gene-environment interactions (so-called multifactorial inheritance).

Evaluation Strategy

Once the diagnosis of CDH has been established, the following approach can be used to try to identify a specific cause of the disorder and to aid in discussions of prognosis and genetic counseling:

CDH should initially be classified phenotypically as being either isolated or complex. These distinctions are made using information from the physical examination, the family history, standard and molecular cytogenetic analyses, imaging studies, and operative or autopsy reports.

- In 50-60% of affected individuals, the CDH is isolated so that no additional congenital abnormalities are detected.
- In the remaining 40-50%, the CDH is complex, which can be further subdivided into those with syndromic CDH (associated with a chromosome abnormality or single gene disorder) or nonsyndromic CDH (associated with additional malformations not occurring as part of a recognized syndrome).

Family history. A three-generation family history with attention to other relatives with multiple congenital anomalies and infants who died in the perinatal period should be obtained. Documentation of relevant findings in relatives can be accomplished either through direct examination of those individuals or by review of their medical records including medical genetics evaluations, results of chromosome analysis, FISH and/or molecular genetic testing, and the results of autopsy examinations.

Physical examination. Infants with CDH should be evaluated by a medical geneticist. Those dying from complications of CDH should undergo an autopsy examination that includes photographs, skeletal x-rays, and a skin biopsy for cell line development.

Testing

- All prenatally and postnatally diagnosed cases of CDH, even those with apparently isolated CDH, should have a standard (550 band) chromosome analysis.
- A high index of suspicion must be maintained when considering the diagnosis of isochromosome 12p (Pallister-Killian syndrome) since peripheral blood chromosome studies are most often normal. The supernumerary 12p is usually present in chromosome analyses performed on non-lymphocyte lineages such as skin fibroblasts, amniocytes, or chorionic villi.
- Prenatally diagnosed CDH cases should routinely have iso12p FISH testing.
- Subtelomeric FISH and array-based comparative genomic hybridization (aCGH) are presently used on a case-by-case basis, especially in the setting of a child with multiple anomalies and/or a suggestive family history. Given the recent reports of aCGH abnormalities detected in individuals with complex CDH and prior normal karyotypes, it is recommended that aCGH is incorporated into the standard laboratory evaluation of such patients. However, data on the diagnostic yield of these newer molecular cytogenetic techniques are not yet available and will only be obtainable after their systematic application to CDH cohorts.

Molecular genetic testing. Testing for specific disorders such as Beckwith-Wiedemann syndrome, Simpson-Golabi-Behmel syndrome, Cornelia de Lange syndrome, and XY sex reversal with renal disorders (which may be caused by *WT1* mutations) (see Wilms Tumor Overview) should be done under appropriate circumstances.

A mutation in *FOG2* has been reported in one person with isolated severe diaphragmatic eventration [Ackerman et al 2005]. Such testing is available on a research basis only.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Congenital diaphragmatic hernia occurs as an isolated finding, as part of a genetic syndrome or chromosome abnormality, or as part of a complex but nonsyndromic set of findings.

If a proband is found to have an inherited or *de novo* chromosome abnormality, a specific syndrome or association with CDH (see Table 2 and Table 3), counseling for that condition is indicated.

Kindreds representing both syndromic and nonsyndromic CDH consistent with autosomal dominant, autosomal recessive, and X-linked patterns of inheritance have been reported. Furthermore, some published pedigrees as well as others [Russell, Ackerman, Pober, unpublished observations] suggest incomplete penetrance.

Empiric Risks to Family Members — Isolated CDH

The majority of individuals with isolated CDH are simplex cases (i.e., the only affected member of the family). A small subset of families are multiplex (i.e., two or more relatives have isolated CDH).

Sibs of a proband

- If a proband is found to have Bochdalek hernia as an isolated finding, the risk to sibs of the proband is generally low (~1-2%); however, families consistent with monogenic inheritance have been reported.
- Based on data from consecutive series, the risk of sibling occurrence for isolated Bochdalek CDH is less than two percent [David & Illingworth 1976, Czeizel & Kovacs 1985, Pober et al 2005]. These studies primarily assessed the frequency of sibs diagnosed with CDH who were born **prior** to the proband; there is no systematic or consecutive series on sibling recurrence to date.
- Based on several case reports of sibling recurrence for diaphragmatic agenesis, it has been suggested that this represents an autosomal recessive variant of CDH. This seems unlikely given that most individuals with diaphragmatic agenesis do not have additional affected family members, that diaphragmatic agenesis is probably on the Bochdalek hernia spectrum (rather than being a distinct entity), and that early case reports of sibling recurrence focused on individuals at the most severe end of the spectrum.

Empiric Risks to Family Members — Complex CDH

Counseling for individuals with complex CDH in whom a specific genetic disorder is not recognized is problematic.

- Some cases of complex CDH are probably caused by new dominant mutations, and therefore pose a low recurrence risk to the sibs of the proband.
- Some are probably unrecognized or private autosomal recessive conditions.
- Some may be multifactorial disorders with a low recurrence risk.
- Non-genetic causes are possible as well, including stochastic events, epigenetic modifications, or teratogenic/environmental exposures.

Thus, counseling in this setting should be as for other multiple congenital anomaly disorders of unknown etiology. Specifically, the estimated recurrence risk to sibs is "low," but this estimate represents an averaging of a negligible, or very low, recurrence risk in the majority of families together with a higher recurrence risk (as high as 25-50%) in the minority of families.

Related Genetic Counseling Issues

Offspring of a proband. Only a small number of adults who are survivors of CDH repair during infancy are currently in their reproductive years. As survival continues to improve, particularly in tertiary care facilities, an increasing number of persons who have had CDH repair will be having children. If new dominant mutations are responsible for a significant proportion of cases with either isolated CDH or nonsyndromic complex CDH, a CDH survivor's risk of having a child with CDH would be as high as 50% if penetrance is complete. Studies will be needed to clarify this issue.

Variable expressivity. The relationship between Bochdalek hernias and muscle migration defects (eventrations) is unknown, but they may be related entities. Both abnormalities have been reported as occurring in different members of the same family and in the same individual [Varpela & Lehtovaara 1969, Thomas et al 1976, Rodgers & Hawks 1986, Mallik et al 1995, Ackerman et al 2005].

Among multiplex families with CDH, concordance is extremely high among affected relatives both for the specific type and the side of the diaphragm defect, although the size of the defect can vary. Very occasionally, one affected sibling has unilateral CDH while a second affected sibling has bilateral CDH or one sibling has an eventration while a second has a diaphragmatic hernia. Also occasionally one sibling has CDH only, while a second affected sibling has CDH plus another common birth defect such as a cardiovascular malformation or polydactyly. Whether these latter cases represent differing manifestations of an autosomal recessive condition or of multifactorial inheritance is not yet known.

Discordant monozygotic twins. Most monozygotic twin pairs described in case reports are concordant for CDH, while those listed in consecutive series generally are discordant (i.e., one member of the twin pair has CDH while the other twin does not) [Pober et al 2005]. A variety of mechanisms, both genetic and non-genetic, can account for these findings [Machin 1996].

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodologies and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the gene(s) or disease-causing mutation(s) has/have not been identified. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Ultrasound examination. The majority of infants with CDH are now diagnosed prenatally by ultrasound examination, which demonstrates herniated viscera with or without liver in the fetal thorax, absence of the normal position of the stomach bubble below the diaphragm, and mediastinal shift [Stege et al 2003, Tonks et al 2004]. Although not specific for CDH, polyhydramnios is often detected [Witters et al 2001].

Calculation of the lung-to-head ratio may be of prognostic value; however, centers have reported mixed results in the utility of this measure for predicting fetal outcome [Lipshutz et al 1997, Laudy et al 2003, Heling et al 2005]. Specifically, the "size" of the right lung is compared to the head circumference; a high ratio (>1.4) indicates good lung size and predicts a good outcome; a low ratio (variously cited as <1.0 or <0.6) indicates small lung size and predicts a poor outcome [Lipshutz et al 1997, Laudy et al 2003]. Some of the limitations of use of the lung-to-head ratio for predicting outcome:

1. Considerable inter-observer variability in determining the lung-to-head ratio
2. An indeterminate ratio of between 1.0 and 1.4 in most fetuses
3. Lower prognostic accuracy with right-sided CDH, with additional birth defects, and/or diagnosis before 24 weeks' gestation or after 26 weeks' gestation.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Color flow Doppler. Color flow Doppler can be used to:

1. Demonstrate abnormal positioning of the umbilical and portal veins, which are indicative of liver herniation
2. Identify right-sided hernias, which can be difficult to detect on ultrasound examination because of the similar echogenicity of lung and liver.

Fetal MRI. Increasingly, fetal MRI is being used to confirm the diagnosis of CDH, as well as to better define the internal anatomy [Hedrick et al 2004]. Calculation of lung volumes using

fast spin-echo MRI appears to provide good prognosis about the degree of pulmonary hypoplasia and subsequent fetal outcome and seems likely to replace the lung-to-head ratio derived from ultrasound examination for this purpose [Gorincour et al 2005].

Other. When CDH is found on routine prenatal ultrasound examination, both a high-resolution ultrasound examination and fetal MRI to determine the presence of additional structural anomalies are indicated. Chromosome analysis of fetal cells obtained by amniocentesis should also be considered. (See Testing for additional details).

All fetuses with CDH should be evaluated for the presence of syndromes and/or additional major malformations given that they so commonly co-exist and significantly affect the prognosis. Involvement of a medical geneticist in the evaluation of these families can be helpful.

Management

Newborns should be intubated immediately in the delivery room to avoid bag-mask ventilation and inflation of the bowel that has herniated into the chest. Care should be taken to not induce barotrauma from bag ventilation before the neonate can be transitioned to an appropriate ventilator.

Over the years, care has shifted from aggressive ventilation with paralysis of the affected infant to "gentle ventilation," as an attempt to minimize the barotrauma induced by positive pressure ventilation. Correction of hypercapnea and pre-ductal hypoxemia are focused on assuring adequate end organ perfusion instead of trying to reach "normal parameters" [Wilson et al 1997, Muratore et al 2001, Boloker et al 2002]. However, treatment of CDH is center-specific [Cacciari et al 2001]. Infants with CDH are now typically treated with minimal sedation and pressure support modes of ventilation, although some centers have had good results using high-frequency oscillatory ventilation (HFOV).

Extra-corporeal membrane oxygenation (ECMO) is frequently used in some centers as a rescue therapy for neonates with critical cardiopulmonary deterioration, but has a limited or non-existent role in other centers. It is unclear whether ECMO improves survival in CDH; Muratore et al (2001) and Stege et al (2003) concluded that the introduction of ECMO did not significantly change mortality. Centers that do not have ECMO report similar survival rates to those that use ECMO, but population biases may play a role in the evaluation of these statistics. When ECMO does rescue an infant who would have otherwise died in the perinatal period, it is unclear whether those infants have good long-term outcome. For these reasons, a randomized controlled trial of ECMO in neonates with CDH is needed [Harrington & Goldman 2005].

The ex-utero intrapartum treatment (EXIT) procedure has evolved as a bridge to ECMO for fetuses with predicted severe CDH or with airway obstruction [Bouchard et al 2002]. This procedure transitions an infant directly onto cardiopulmonary bypass when oxygenation and ventilation by intubation and mechanical ventilation are not expected to be possible. Although it is clear that this procedure is indicated for airway occlusions, it is difficult to predict which infants with CDH should be eligible based on severity of prenatally predicted pulmonary hypoplasia.

Other therapies that have been introduced in the acute neonatal treatment phase for CDH include nitric oxide (NO) [Okuyama et al 2002], decision to delay surgical repair [Moyer et al 2002], and use of surfactant and perflubron [Fauza et al 2001, Hirschl et al 2003]; however, the lack of randomized controlled trials make it difficult to determine which of these treatments may be beneficial.

Infants who develop pulmonary hypertension are more difficult to treat and have decreased survival, making control of pulmonary hypertension a reasonable goal [Dillon et al 2004].

Fetal surgery has evolved as a treatment strategy for severely affected infants. The discovery that laryngeal obstruction leads to lung distension from retained fluid prompted tracheal occlusion studies in animal models and in humans [Alcorn et al 1977, Lipshutz et al 1997, Harrison et al 2003]. In one US randomized trial of fetal endoscopic tracheal occlusion, the treatment group suffered from a high rate of pre-term delivery and did not have improved morbidity or mortality rates [Harrison et al 2003]. However, a European multicenter study in which a deflatable balloon was inserted in the second trimester to achieve tracheal occlusion showed some promising results [Deprest et al 2005].

Following surgical correction and hospital discharge, long-term follow-up for infants with CDH is ideally provided at a specialized center by a multidisciplinary team consisting of a pediatric surgeon, surgical nurse specialist, cardiologist, nutritionist, pulmonologist, and developmental pediatrician. This type of team can recognize, treat, and coordinate care for the many medical complications frequently found in long-term survivors with CDH.

Animal models of CDH. For information on animal models used for studying CDH, click here.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

CHERUBS-The Association of Congenital Diaphragmatic Hernia Research, Advocacy, and Support
270 Coley Road
Henderson, NC 27537
Phone: 252-492-6003
Fax: 815-425-9155
Email: info@cherubs-cdh.org
www.cherubs-cdh.org

Medline Plus
Diaphragmatic hernia

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 1 February 2006 (me) Review posted to live Web site
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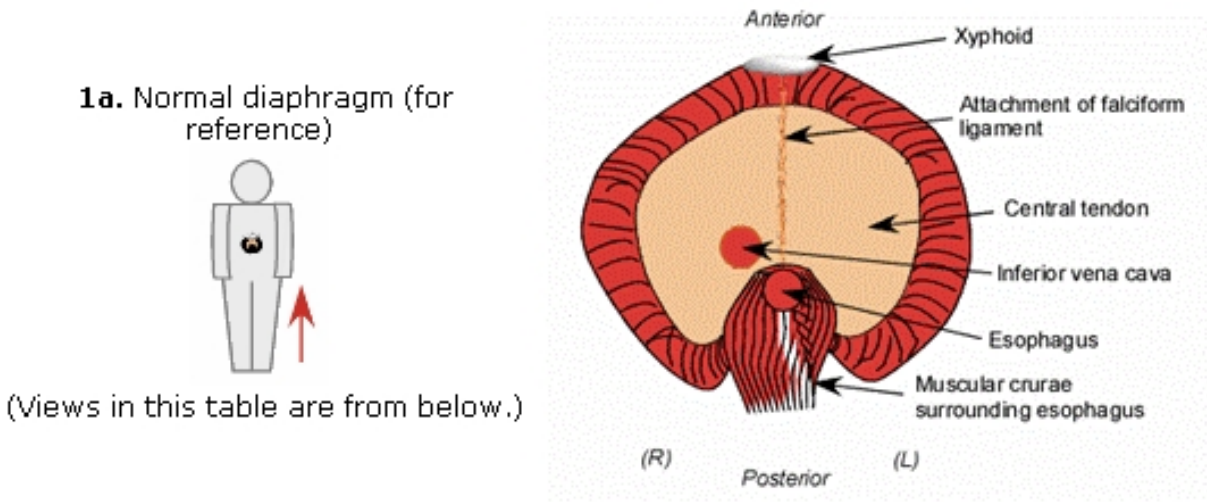

Figure 1. View of normal diaphragm from below

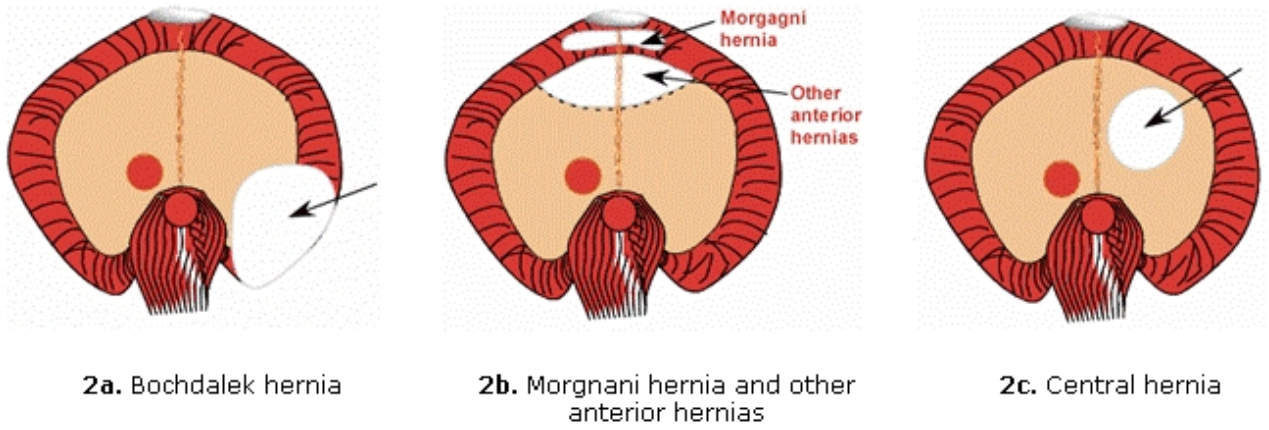

Figure 2. View of diaphragmatic defects from below